REMARKS

Status of the Claims

Claims 1-3, 8-13, 19, 20, 29-31 and 39-48 are in the application.

Claims 1-3, 8-13, 19, 20, 29-31, 39, 41, 42, 44, 45, 47 and 48 were rejected.

Claims 41, 42, 44, 45, 47, and 48 have been amended and new claims 49-61 have been added.

Upon entry of this amendment, claims 1-3, 8-13, 19, 20, 29-31 and 39-61 will be pending.

Summary of the Amendment

A replacement sequence listing has also been submitted and incorporated into the present specification. The specification has also been amended to include sequence identifiers. The sequences are the sequences that were referred to by the accession numbers listed in paragraph 51. Claims 41, 42, 44, 45, 47, and 48 have been amended to recite that CDX1 is encoded by an identified sequence. Claims 49-61 have been added and are directed to methods of diagnosing and in vitro screening relating to CDX1 expression or transcription in metastatic colorectal cancer. Support for these amendments can be found throughout the specification and the claims as-filed.

No new matter has been added.

Objections

Claims 41, 42, 44, 45, 47, and 48 stand objected to because the claims allegedly incorporate essential material in the specification by reference. Applicants have amended the specification to include the sequences by referring to sequence identifiers and amending the sequence listing to include the sequences disclosed by the accession numbers. Applicants have also submitted herewith a declaration executed by the undersigned stating the amendatory

material consists of the same material incorporated by reference in the referencing application. No new matter has been added by introduction of the sequences into the sequence listing.

In view of the foregoing, Applicants respectfully request that the objection be withdrawn.

Claims 40, 43, and 46 stand objected to as being dependent upon a rejected base claim. In view of the arguments presented herein Applicants respectfully assert that claims 40, 43, and 46 no longer depend upon a rejected base claim.

In view of the foregoing, Applicants respectfully request that the objection be withdrawn.

Claim Rejection Under 35 U.S.C. § 112, first paragraph

Claims 41, 42, 44, 45, 47, and 48 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. The Office alleges that the specification incorporates essential material by reference and that the Genbank database could be inoperable thereby rendering the claims non-enabled. In view of the amendments to the specification and the sequence listing, the allegedly essential material is no longer incorporated by reference. Applicants have also submitted herewith a declaration executed by the undersigned stating the amendatory material consists of the same material incorporated by reference in the referencing application. No new matter has been added by introduction of the sequences into the sequence listing.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim Rejection under 35 U.S.C. § 103

Claims 1-3, 8-13, 19, 20, 29-31, and 39 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Silberg *et al.* (Gasteroenterology, 1997 Aug; 113(2):478-86) in view of U.S. Patent No. 5,601,990. Claims 41, 44, and 47 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Silberg in view of the '990 patent and further in

view of GenBank Accession No. U51095. Claims 42, 45, and 48 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Silberg in view of the '990 patent and further in view of GenBank Accession No. U15212.

The Office alleges that Silberg reports CDX1 protein being detected in stomach or esophageal cancer tissue. The Office admits that Silberg fails to teach a method of detecting CDX1 in extraintestinal tissue and/or body fluids. The Office alleges that the '990 patent reports that extraintestinal tissue and/or body fluids can be used to detect a biomarker and the detection of such biomarker for cancer is associated with metastasis. Thus, the Office alleges that "it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success sine Silberg *et al.* teach that CDX1 is a biomarker 'involved in the neoplastic process' . . . and US 6501990 teaches how to use extraintestinal tissue and/or body fluids for a biomarker for metastatic cancers." (Office Action, page 5). Applicants respectfully disagree.

The claimed invention is not obvious. The Office has failed to put forward a proper *prima facie* obviousness rejection because the Office has not articulated a reasonable explanation as to why the claims are obvious other than through the use of conclusory statements. The Office has also failed to demonstrate that one of skill in the art would have had a reasonable expectation of success in diagnosing or screening for metastasized esophageal, stomach or colon cancer based upon the cited references. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." M.P.E.P. § 2141 (quoting *KSR*). "Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have

prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR at* 1741 (2007).

The combination of the cited references fails to render the claims obvious because the combination fails to suggest the claimed invention and, even if combined, the references fails to provide a reasonable expectation of success regarding the detection of CDX1 expression in extraintestinal tissue or body fluids of patients who have metastatic esophageal, stomach, or colorectal cancer. Silberg reports CDX1 protein expression in different types of the human alimentary tract epithelium. Silberg fails to disclose or suggest analyzing extraintestinal tissue or body fluids for the expression of CDX1 to detect metastasized cancer cells. The Office alleges that the '990 patent cures Silberg's deficiency because the '990 patent discloses the detection of a biomarker (*e.g.* ST receptor protein) in extraintestinal tissue and/or body fluids. The Office, however, has not explicitly stated why one would combine the references other than the facts that the elements exist. Furthermore, the elements that are combined do not produce the claimed invention.

The obviousness rejection is improper because Silberg fails to discuss whether CDX1 is even expressed in metastasized cells that are present in extraintestinal tissue and/or body fluids. Silberg reports the expression in intestinal metaplasia. A metaplastic cell is not the same as a metastasized cell. Metaplasia refers to a change of a cell to a form that does not normally occur in the tissue in which it is found. (See, Attached definition, found at National Cancer Institute's webstite "Dictionary of Cancer Terms", www.cancer.gov/Templates/db_alpha.aspx?CdrID=45786). Metaplasia is not elated to the cell's location. The present specification defines metastasized in terms of each cancer type. For example, the specification states:

> As used herein, the term "metastasized colorectal cancer cells" is meant to refer to colorectal cancer cells which have metastasized. Metastasized colorectal cancer cells localized in a part of the body other than the duodenum, small intestine (jejunum and ileum), large intestine (colon), including the cecum, ascending

> colon, transverse colon, descending colon, and sigmoid colon, and rectum.
>
> As used herein, the term "metastasized stomach cancer cells" is meant to refer to stomach cancer cells which have metastasized. Metastasized stomach cancer cells localized in a part of the body other than the stomach.
>
> As used herein, the term "metastasized esophageal cancer cells" is meant to refer to colorectal cancer cells which have metastasized. Metastasized esophageal cancer cells localized in a part of the body other than the esophagus.

(Specification, paragraphs 34-36). The metaplastic cells referred to in Silberg have not metastasized. The Office has failed to explain why one of skill in the art would substitute CDX1 for the biomarker described in the '990 patent. The reasoning provided by the Office completely omits any mention as to why one skilled in the art would expect that the CDX1 disclosed in Silberg could be used in the same manner as the biomarker in the '990 patent. Rather, the position taken by the Office presumes those skilled in the art would *a priori* expect that CDX1 as taught in Silberg and the biomarker in the '990 patent are interchangeable. Applicants respectfully urge that such a presumption is improper and, accordingly, a prima facie case for obviousness has not been established.

The generalized statements that because one reference is able to detect a biomarker in extraintestinal tissue and/or body fluids can be applied to any gene or gene product is not supported by sufficient evidence to maintain the obviousness rejection. There are many genes that are expressed in cancer cells but the present invention identified CDX1 as one that can be found in a metastasized cell that is found in a sample from extraintestinal tissue and/or body fluids. Both Silberg and the '990 patent are silent when it comes to this feature regarding CDX1. The lack of support for a *prima facie* obviousness rejection is not cured by the GenBank references cited in the rejection of claims 41, 42, 44, 45, 47, and 48 because they are used only to supply the sequences of CDX1. Accordingly, the *prima facie* rejection is improper.

Even if there were a sufficient reason to combine the references the Office has failed to show that there would be a reasonable expectation of success. The Office states that there would have been a reasonable expectation of success because Silberg reports that CDX1 "may be involved in the neoplastic process" (Silberg, p. 479, left column, last paragraph). Silberg, however, fails to report any conclusion or connection with respect to whether CDX1 is expressed in metastasized cells. Conclusory statements regarding the expectation of success are not sufficient to find the claims obvious.

The combination of the references fails to create a reasonable expectation of success because Silberg reports that CDX1 expression is not consistently detected in all metaplastic cells, let alone metastasized cells present in a sample from extraintestinal tissue and/or body fluids. For example, Silberg reports that in some metaplastic cells there were cells that had negative staining for CDX1. Therefore, one of skill reading the Silberg reference as a whole would not have a reasonable expectation of success for using the presently claimed methods to detect CDX1 in metastasized cells because based upon Silberg it is not clear whether CDX1 can always be detected. A reasonable expectation of success is not created by the Genbank references cited because the Office has not explained why the disclosure of a sequence would lead one of skill in the art to be able to expect to detect CDX1 in samples taken from extraintestinal tissue and/or body fluids.

Further evidence that Silberg does not provide a reasonable expectation of success can be found in Silberg because Silberg teaches away from using CDX1 as a marker in metastasized colorectal cancer cells. Silberg reports that "normal colonic epithelium stained intensely" for CDX1 while the staining decreased as the cells became more transformed. (Silberg, p. 482. right column, first full paragraph). Additionally, Silberg reports that "some adenocarcinomas of the colon were devoid of CDX1 expression, whereas others had a small amount of staining." (Silberg, p. 482. right column, first full paragraph) Silberg did not evaluate metastasized colorectal cancer cells in a sample from extraintestinal tissue and/or body fluids. Silberg's reporting that colon adenocarcinomas had decreased CDX1 expression or CDX1 expression

could not be detected would lead one of skill in the art to not use CDX1 as a biomarker because of its inconsistent expression. Therefore, Silberg teaches away from using CDX1 as a biomarker for metastasized colorectal cancer. The Genbank references cited by the Office do not contradict Silberg teaching away from the claimed invention. Therefore, the claims, including new claims 49-53, are not obvious.

Accordingly, the claims are not obvious because the Silberg references fails to discuss CDX1 in metastasized cells that could be detected in extraintestinal tissue and/or body fluids and the combination does not suggest the claimed invention. Furthermore, the Office has failed to articulate with sufficient evidence that there would have been a reasonable expectation of success in view of Silberg's reporting uneven CDX1 expression in esophageal and intestinal cells and decreasing expression in colorectal cancer cells. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

Claims 1-3, 8-13, 19, 20, 29-31 and 39-61 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7820 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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